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Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy:

A Scientific Statement from the American Heart Foundation

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Abstract

Hypertensive disorders of pregnancy (HDP) remain one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Affected women are also at increased risk for cardiovascular disease (CVD) later in life, independent of traditional CVD risks. Despite the immediate and long-term CVD risks, recommendations for diagnosis and treatment of HDP in the United States have changed little, if at all, over past decades, unlike hypertension guidelines for the general population. The reasons for this approach include the question of benefit from normalization of blood pressure treatment for pregnant women, coupled with theoretical concerns for fetal well-being from reduction in utero-placental perfusion and *in utero* exposure to antihypertensive medication.

This report is based on a review of current literature and includes: normal physiological changes in pregnancy that may affect clinical presentation of HDP; HDP epidemiology and their immediate and long-term sequelae; the pathophysiology of preeclampsia, a HDP commonly associated with proteinuria and increasingly recognized as a heterogeneous disease with different clinical phenotypes and likely distinct pathological mechanisms; a critical overview of current national and international HDP guidelines; emerging evidence that reducing blood pressure treatment goals in pregnancy may reduce maternal severe hypertension without increasing the risk of pregnancy loss, high level neonatal care or overall maternal complications; and the increasingly recognized morbidity associated with postpartum hypertension/preeclampsia. Finally, we discuss the future of research in the field and the pressing need to study socioeconomic and biological factors that may contribute to racial and ethnic maternal health care disparities.

1.0 Introduction

Hypertensive disorders of pregnancy (HDP) encompass chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension.[1] The diagnostic criteria for HDP in the U.S. have evolved over the past 5 decades;[1] (Table 1) the most current definition of hypertension in pregnancy from the

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American College of Obstetricians and Gynecologists (ACOG) was published in 2013,[1] with updates and recommendations made in 2019 and 2020.[2, 3]

Most guidelines around the world are aligned in defining hypertension in pregnancy as BP ≥140/90 mm Hg (Table 6, has all the references). There is variability regarding the threshold for initiating antihypertensive treatment due to uncertainty about the maternal benefits of lowering blood pressure (BP) and the potential fetal risks from medication induced reductions in utero-placental circulation and *in utero* exposure to antihypertensive medications.[2] In contrast, diagnostic and treatment thresholds for the general population have evolved over the years;[4, 5] the 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults threshold for the diagnosis of Stage 1 hypertension was further lowered to 130/80 mm Hg, from 140/90 mm Hg,[6] based on observational studies and clinical trials demonstrating reduced CVD events with treatment to lower levels.[7, 8]

This scientific report presents a synthesis of the scientific evidence (from literature published until August 31st, 2020) that is relevant to the current controversies regarding HDP diagnostic and treatment strategies. It is a timely statement given that current trends indicate the incidence of HDP continues to increase[9, 10] due to advanced age at first pregnancy, and increased prevalence of obesity and other cardio-metabolic risk factors. Cardiovascular disease, including cerebrovascular accidents and cardiomyopathy, now account for approximately half of all maternal deaths.[11] Pregnancy related stroke hospitalizations increased more than 60% from 1994 to 2011 and HDP associated stroke rates increased 2-fold compared to non-HDP related stroke.[10] Thus, in the discussion that follows, we emphasize the need for future research aimed at recognizing and appropriately treating HDP.

2.0 Epidemiology

The HDP are the second leading cause of global maternal mortality behind maternal hemorrhage[12] and are a significant cause of short and long-term maternal morbidity. HDP are also associated with adverse fetal outcomes (Tables 2 and 3). Elevated systolic BPs throughout pregnancy, even below the diagnostic threshold for hypertension are also associated with increased risk of pre-term delivery, small for gestational age, and low birthweight.[13, 14]

Traditionally, incidence of HDP was reported on a per-pregnancy basis to assist prediction of pregnancy-related complications (both maternal and fetal) in an obstetric clinical setting (Table 2).

However, the HDP population-based incidence expressed per-pregnancy (7.5%) underestimates the number of women affected by this condition during their reproductive years (15.3%).[23] Per-women rather than per-pregnancy incidence provides better assessment of the number of women at risk for future CVD based on their reproductive histories,[24] including development of diabetes and hypertension[23, 25] (Table 3).

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It is well accepted that hypertension develops significantly more frequently after HDP, but studies indicate that hypertension also develops faster and is diagnosed up to 10 years earlier compared to women with normotensive pregnancies,[23, 30, 46–48] though the precise timing requires further examination. Earlier onset of cardio-metabolic risk factors and CVD events,[26, 34, 46] as well as higher rates of accumulated chronic conditions and multi-morbidity,[23] support the thesis of accelerated aging among women who have a history of HDP.[23, 25, 49]

3.0 Pathophysiology of HDP

3.1 Hemodynamic Changes in Normal Pregnancy and Preeclampsia

Systemic vascular resistance decreases while plasma volume and cardiac output increase during pregnancy. There is a physiological drop in BP, often detectable before the end of the first trimester,[50, 51] due to vasodilation.[52] Meta-analyses and high quality longitudinal studies found that compared to BP at 10 or 12 weeks, the BP drop during the second trimester was on average 1–2 mm Hg.[53–55] There is wide inter-individual variability and BP trajectories likely relate to pre-existing maternal health factors,[55] such as chronic hypertension, and require further clarification. Renal blood flow and glomerular filtration rate increase by 50% in normal pregnancy, but are approximately 30% lower in women with preeclampsia as a result of both decreases in renal blood flow and the ultrafiltration coefficient, attributable to endotheliosis in the glomerular capillary bed.[56] Plasma volume increases in normal pregnancy, and earlier studies have suggested that it may be decreased in women with preeclampsia.[57] However, multiple longitudinal and cross-sectional studies in preeclamptic women demonstrating suppressed plasma renin activity, high blood pressure, decreased glomerular filtration rate and frequent development of edema are more consistent with an overfilled, vasoconstricted circulation rather than true hypovolemia and underfilling.[58] Cardio-metabolic changes in normal pregnancy are more pronounced in women who develop preeclampsia and include increased insulin resistance, total cholesterol, triglycerides, HDL-C and LDL-C.[59] Hypercoagulability, a feature of normal pregnancy, may be exaggerated in preeclampsia and is caused by increased thrombin generation, fibrinogen, and activated protein C resistance, and reduced protein S and fibrinolysis.[60]

3.2 Abnormal Placentation and the Pathogenesis of the Maternal Preeclampsia Syndrome

The diameter of the uterine spiral arteries increase greatly during normal pregnancy due to remodeling of the endothelium and vascular smooth muscle, stimulated by release of proteases from endovascular trophoblast and uterine Natural Killer cells.[61] Failure of spiral artery remodeling (i.e., retention of smooth muscle) is a feature of preeclampsia (Figure1)[62, 63] and leads to decreased utero-placental perfusion, demonstrated by non-invasive blood flow and perfusion studies using Doppler ultrasound or magnetic resonance imaging.[63]

Placental pathology due to rheological consequences includes villous architectural changes due to turbulent jets entering the intervillous space at rates of 1–2m/s (10–20 times normal), causing the rupture of anchoring villi and formation of echogenic cystic lesions that are visible by ultrasound.[66] In addition, retention of vascular smooth muscle preserves the

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ability of spontaneous vasoconstriction and ischemia-reperfusion injury, which may result in oxidative stress.

Alterations in angiogenic factors are recognized as a likely consequence of abnormal placentation occurring in early pregnancy. Increased circulating soluble fms-like tyrosine kinase 1 (sFlt1), an anti-angiogenic factor of placental origin, leads to neutralization and decrease of pro-angiogenic factors, such as placental growth factor (PlGF) and vascular endothelial growth factor, which then contribute to the hypertension and glomerulopathy characteristic of the maternal syndrome.[63] Measurements of angiogenic biomarkers have been incorporated into risk stratification in several innovative therapeutic trials for preeclampsia prevention,[67, 68] but are not routinely used to guide clinical care in most countries, including the US. An increased sFlt1/PlGF ratio may be particularly pronounced in women with early, (<34 gestational weeks) severe preeclampsia, which has been designated by some as placental preeclampsia[69] because of the association between placental ischemia and adverse fetal outcomes (fetal growth restriction, in particular). Preeclampsia occurring later in pregnancy, labeled by some as maternal preeclampsia, has been associated with more pronounced maternal vascular dysfunction prior to pregnancy (secondary to hypertension, diabetes, or obesity), less pronounced placental pathology, and fewer fetal complications. In maternal preeclampsia, pregnancy acts as a physiological stress test that exacerbates preexisting endothelial dysfunction. This underscores the heterogeneity of HDP, whereby the extremes of clinical subtypes (early versus late, mild versus severe, and presence or absence of fetal growth restriction) may reflect distinct underlying mechanisms.[69] Sharp discrimination between maternal vs. placental preeclampsia is overly simplistic and artificial as both processes likely play a role, but with varying contributions. Regardless of the clinical subtype, diagnosis and treatment of hypertension remains a mainstay of the prevention of immediate maternal complications and permanent cardiovascular injury, together with seizure prevention using magnesium sulfate.

4.0 Prevention of preeclampsia and adverse maternal and fetal outcomes

Preconception health, and its impact on both pregnancy outcomes as well as future health, has gained attention.[70] Lifestyle changes before and during pregnancy may ameliorate both maternal and fetal risks. A meta-analysis of 44 randomized controlled trials reported that dietary interventions reduce maternal gestational weight gain and improve pregnancy outcomes.[71] Exercise may reduce gestational hypertension and preeclampsia risk by approximately 30 and 40%, respectively.[72, 73] The first Canadian guideline for physical activity throughout pregnancy published in 2019 recommends that all women without contraindication should be physically active during pregnancy.[74] Low dose aspirin, starting between 12 and 16 weeks of gestation, reduces the risk of preeclampsia and related adverse outcomes by 10 to 20% in women at increased risk (Table 4).[75–78] ACOG recommends daily low dose aspirin for women with a history of early onset preeclampsia and preterm delivery, or for women with more than one pregnancy complicated by preeclampsia.[77]

The optimal dose of aspirin has not been formally tested, with most trials using 81 to 150 mg daily.[76] Promising results from experimental studies and a pilot trial of pravastatin[104, 105] need to be critically viewed due to concerns related to fetal safety.

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Experimental evidence suggests that metformin may prevent preeclampsia by reducing sFlt1 and soluble endoglin secretion from primary endothelial tissue and through senomorphic mechanims.[106, 107 65] Clinical studies have indicated that metformin may reduce the odds of gestational hypertension in women with gestational diabetes, and that it may prevent preeclampsia.[108]

5.0 Blood pressure measurement in pregnancy

Accurate BP measurement is crucial for classifying hypertension and initiating treatment, regardless of pregnancy status. As mercury sphygmomanometers are less available, aneroid devices are commonly used, although they require calibration and are less accurate. Several oscillometric automated devices have been validated in pregnant women, including those with gestational hypertension and preeclampsia.[109]

While most current guidelines recommend hypertension management based on office BP in pregnancy, for the general population, out of office BP measurements are widely endorsed as more accurate and better predictors of cardiovascular morbidity and mortality.[6, 110] Although several studies report BP levels during pregnancy using self-measured BP (SMBP) or ambulatory BP monitoring (ABPM), current data describing appropriate out of office cut offs for HDP diagnosis are limited.[111] American College of Obstetricians and Gynecologists and the International Society for the Study of Hypertension in Pregnancy (ISSHP) recommend the use of SMBP in women with chronic or gestational hypertension, particularly when uncontrolled.[1, 112] Available information does not demonstrate a systematic difference between self and office BP measurements in pregnancy, which suggests appropriate treatment and diagnostic thresholds for self-monitoring during pregnancy may be equivalent to standard clinic thresholds; however, additional information regarding appropriate methodology and validation of devices is needed.

5.1 Non-sustained hypertension

White coat hypertension is reported in 25% of the non-pregnant adult population. Its prevalence in pregnancy is less certain, ranging from 4 to 30%.[2] On the basis of 24 hour BP measurements, 32% of hypertensive women had white-coat hypertension, but just 8% were diagnosed as such.[113] A meta-analysis of studies addressing white coat hypertension reported increased risks of preeclampsia and adverse fetal outcomes compared to women with normotension. Risks were lower compared to women with sustained chronic or gestational hypertension.[87] The frequency and clinical significance of masked hypertension in pregnancy has not been extensively studied. Any category of non-sustained BP elevation in pregnancy can progress to sustained hypertension and requires follow-up. Self-measured BP is important for diagnosing non-sustained BP elevations, including masked hypertension and white coat hypertension which occur prior to 20 weeks of gestation. For clinical purposes, the definition of hypertension in pregnancy requires two elevated BP four hours apart (Table 1).

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5.2 Blood pressure variation

In the non-pregnant population, the association between BP variation, independent of baseline BP, and CVD risk is mixed, although greater variability is more convincingly associated with increased stroke risk.[114–120] Limited small studies of gestational short-term and visit-to-visit BP variation suggest that greater variation is associated with adverse maternal and perinatal outcomes,[121, 122] but evidence is currently inconclusive and there is need for consensus regarding the methodology for the measurement of BP variability in pregnancy.

Standard gestational age-specific BPs and centiles can assist in clinical interpretation of BP changes from expected levels.[55, 122] Nationally representative, population-specific, gestational BP references have been reported from China and the United Kingdom.[51, 53] Studies addressing the association of BP changes in relation to healthy BP standards with maternal and perinatal outcomes are needed.

5.3 Secondary hypertension

Most (~90%) women with chronic hypertension have primary hypertension. Secondary hypertension may occur in a small proportion of women and is associated with worse maternal and fetal outcomes; it should be considered if: maternal age is <35 years, hypertension is severe or resistant, there is no family history of hypertension, or there are suggestive laboratory features, such as hypokalemia, elevated creatinine, or albuminuria early in pregnancy (Table 5).[123, 124] Finally, the prevalence of obesity in reproductive-aged women has increased in recent years and obstructive sleep apnea may play an increasing role in secondary hypertension among pregnant women.[125, 126] As there are no pregnancy-specific guidelines for obstructive sleep apnea treatment, pregnant women with sleep apnea should be managed concurrently with a sleep medicine specialist for application of available diagnostic and therapeutic methods depending on the stage of pregnancy.

5.4 Postpartum hypertension and postpartum preeclampsia

Postpartum hypertension and postpartum preeclampsia are not specifically included in the classification of HDP, but there is increasing awareness of their significance, as documented in the 2013 ACOG executive summary that implemented changes in clinical practice through closer postpartum monitoring and visits.[127] These entities are particularly important for two reasons. First, roughly 80% of all maternal deaths occur within the first week postpartum, and HDP remain one of the leading causes of maternal mortality.[128] Second, postpartum hypertension offers an opportunity to use medications and achieve BP goals without limitations related to their potential negative impacts on the fetus. The prevalence of postpartum hypertension may be as high as 8% in women without antepartum hypertension (followed 48 hours after delivery and up to 6 weeks postpartum), and up to 50% in women with a history of preeclampsia 6–12 weeks post-delivery.[129, 130] The distinction between postpartum aggravation of antepartum HDP and *de novo* postpartum preeclampsia (also termed, delayed onset postpartum preeclampsia) is unclear. Further research addressing underlying mechanisms is needed to clarify appropriate treatment and need for magnesium sulfate for seizure prevention. The duration ranges from days to 3 months, contributing to serious short term maternal complications such as stroke, seizures and cardiomyopathy, and

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metabolic dysregulation such as insulin resistance and weight gain.[129, 130] Patient education is an important tool for early recognition of symptoms and signs. Novel approaches such as remote hypertension monitoring programs have potential to improve compliance and early diagnosis of postpartum hypertension and preeclampsia.[131]

The rate of elevation in the antepartum sFlt1/PlGF ratio is an independent predictor of hypertension that persists postpartum.[132] Furthermore, preeclampsia associated endothelial dysfunction and altered cerebrovascular autoregulation have been shown to persist postpartum[133] and may amplify postpartum hypertension risk. Intravenous fluids, mobilization of extravascular fluid and use of nonsteroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may contribute to its occurrence. A recent randomized controlled clinical trial has shown that postpartum use of furosemide in women with HDP was associated with a 60% reduction in persistent hypertension at day 7 following delivery (adjusted relative risk 0.40).[134] If these findings can be implemented in the clinic, there is significant opportunity to reduce maternal morbidity in the postpartum period and avoid unnecessary hospitalization. In non-pregnant individuals, there is abundant evidence that NSAIDs are associated with clinically significant increases in BP.[135–137] A recent systematic review and meta-analysis that included 5 randomized controlled trials and 5 retrospective cohorts concluded that compared to acetaminophen, NSAIDs were not associated with increased BPs up until discharge (2 to 4 days postpartum).[138] The authors considered the quality of evidence to be very low because of the small sample sizes, imprecise results and short duration of follow up. Additional investigation is needed to address the impact of longer duration of postpartum NSAID use in older women with chronic hypertension and additional renal and cardiovascular risk factors.[139, 140]

6.0 Treatment of Hypertension in Pregnancy

6.1 Current blood pressure goals for pregnant patients

The recent ACC/AHA task-force guidelines lowered the threshold for the diagnosis of hypertension in non-pregnant patients to 130/80 mm Hg for stage 1 hypertension, and 140/90 mm Hg for stage 2 hypertension, resulting in larger numbers of individuals being diagnosed and treated.[6] There is robust evidence in the general population demonstrating reduced CVD risk with treatment to lower levels,[7] and indeed, most cardiovascular events occur in individuals with BP levels of 140–159/90–109 mm Hg.[141] Even younger individuals with hypertension demonstrate early vascular remodeling and endothelial dysfunction, particularly in smaller arteries and arterioles, which leads to progressive stiffening of larger blood vessels and organ damage if hypertension is untreated.[142, 143] For all HDP, hypertension is defined internationally as a BP ≥140/90 mm Hg, though treatment thresholds and targets vary (Table 6).

The recommendations of published guidelines addressing diagnosis and treatment of HDP are summarized in Table 6. Differences among societies further demonstrate confusion in the field, which likely contributes to a failure to move forward. The ACOG recommends antihypertensive therapy for women with preeclampsia and a sustained systolic BP ≥160 mm Hg and/or diastolic BP ≥110 mm Hg, and with chronic hypertension at a systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg, with a treatment goal of 120–160/80–110

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mm Hg.[2] Internationally the majority of hypertension societies endorse a more aggressive approach for antihypertensive treatment, recommending therapy when BP is ≥140/90 mm Hg.[112, 144–146, 152, 154] Therapeutic targets similar to the ACC/AHA target of 130/80 mm Hg[6] are recommended by the ISSHP,[112] Hypertension Canada Guidelines,[148, 152] NICE,[146] and the WHO.[145] The question arises: why are the diagnostic and treatment BP thresholds higher in the U.S. compared to those recommended for non-pregnant individuals and in comparison to the majority of international guidelines addressing HDP?

Determining the optimal BP threshold in pregnancy for antihypertensive treatment and therapeutic targets requires a balance between prevention of maternal hypertensive complications and avoidance of fetal risks. The US (ACOG) guidelines are influenced by at least three debated issues. First, is the prevailing perspective, based on small studies, that there are no measurable immediate or long-term health benefits of more strict BP treatment for the relatively short duration of pregnancy (4 to 9 months, depending on type of HDP) in young women without other CVD risks. Second, there are concerns that lowering maternal BP may compromise utero-placental circulation and negatively affect fetal well-being and growth. Third, therapeutic options are limited due to concerns regarding potential adverse fetal effects, particularly malformations from intrauterine exposure to antihypertensive medications. Furthermore, discrepancies among international guidelines are a reflection of the country specific context within which they were developed. Such debate and subsequent inconsistencies in recommendations hinder progression towards consensus for optimal management of HDP internationally. For example, differences in BP thresholds for initiating antihypertensive therapy make combining results from observational studies of antihypertensive therapy for meta-analysis more challenging.

6.2 Blood pressure goals for pregnant patients: emerging data, limitations and current controversies

There are several compelling reasons to consider lower BP thresholds. First, more aggressive treatment of hypertension in pregnancy prevents the development of severe hypertension, as demonstrated by both a systematic review of randomized trials[155] and the Control of Hypertension In Pregnancy Study trial (CHIPS), in which the average BP achieved by tight control was 133/85 mmHg.[16] While comparison of less tight versus tight control showed no effect on rates of preeclampsia, the former group demonstrated a higher risk of thrombocytopenia and elevated liver-enzyme levels, markers of disease severity. Also, in this trial and elsewhere, ‘tight’ control may have decreased the risk of preterm birth.[156] The importance of severe hypertension as an outcome has been questioned,[22] although exploratory analyses of the CHIPS data (adjusted for allocated group and prognostic factors) showed that severe hypertension is a surrogate marker for adverse maternal and perinatal outcomes, independent of and similar in magnitude to preeclampsia.[16, 22] This is especially relevant in high risk populations, such as Black women, for whom the risk of hypertension related adverse outcomes is high.[157] A study of Black women with chronic hypertension showed that use of antihypertensives prior to 20 weeks of gestation and achieving a BP <140/90 mm Hg was associated with lower incidences of superimposed preeclampsia and preterm delivery <35 weeks compared to women with BP ≥140/90 mm Hg.[158] Furthermore, lower (<140/90 mm Hg) versus higher (≥140/90 mm Hg) BP levels during pregnancy

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have been associated with lower rates of preeclampsia, including preeclampsia with severe features, and lower rates of pre-term delivery.[156] Lower rates of preeclampsia with treatment of hypertension reported by these most recent studies are in sharp contrast with the majority of previous studies indicating that treatment of hypertension does not prevent preeclampsia. Whether there is a difference between women with chronic (who were preferentially recruited in these 2 studies indicating benefit) versus gestational hypertension, remains unknown; the answer will require prospective, adequately powered studies. Based on results of retrospective studies, including one showing benefit of tighter BP control,[159] and the other indicating that malignant/uncontrolled hypertension in the non-pregnant state has similar changes in the brain as eclampsia,[160] a large randomized controlled trial The Chronic Hypertension and Pregnancy (CHAP) Project is nearing completion in the United States (ClinicalTrials.gov Identifier: NCT02299414) comparing outcomes between pregnant, chronically hypertensive women who are given antihypertensive treatment to maintain BP <140/90 mm Hg, to women given no treatment, unless BP is ≥160/105 mm Hg.

Second, there is evidence that the pathophysiology of the neurologic manifestations (headaches, visual disturbances, seizures) of preeclampsia is similar to that of the posterior reversible leukoencephalopathy syndrome.[161] Women with preeclampsia may be more susceptible to severe neurologic outcomes, such as intracerebral hemorrhage, at lower systolic BPs (e.g. 150–170 mmHg)[162] compared to non-pregnant subjects, thus raising the possibility that lowering BP below current targets (e.g., <150/90 mm Hg) may prevent these rare but devastating outcomes.[162]

Third, treatment of non-severe hypertension in pregnancy (e.g. BPs 140–155/90–109 mm Hg) may permit prolongation of pregnancy in women without other severe features of preeclampsia that would require delivery.

Fourth, ACOG guidelines recommend withholding antihypertensive therapy for patients with preeclampsia unless BP approaches 160/110 mm Hg. They also recommend urgent delivery for women with severe features of preeclampsia, which include uncontrollable HTN with BP ≥160/ 110 mm Hg, even for pregnancies < 34 gestational weeks, unless high level care is available in facilities with adequate maternal and neonatal intensive care resources.[3, 112, 163] Lowering thresholds for treatment may allow for timely BP control and avoidance of rushed deliveries that commonly lead to prematurity and related complications.

Fifth, the classical view that young, hypertensive women without other CVD risk factors are at low short term CVD risk from untreated hypertension during the duration of pregnancy, is challenged by current epidemiological and demographic trends towards advanced age at first pregnancy and higher CVD risk (subclinical or diagnosed).[164–167] This could also be relevant among women with multiple pregnancies, who may spend several years of their lives either pregnant or breastfeeding with uncontrolled hypertension. In addition, modern fertility techniques facilitate pregnancy in women with pre-existing conditions associated with elevated CVD risk (e.g., diabetes, chronic kidney disease, and polycystic ovary syndrome). Pre-existing chronic kidney disease and heart disease are present in 3% and 1–4% of pregnancies in high income countries, respectively.[168] Several guidelines consequently endorse more aggressive treatment in these women.[150, 151]

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Finally, there is abundant evidence that HDP are associated with increased risk of both immediate and postpartum complications (such as acute cardiovascular and cerebrovascular disease)[169] and future maternal vascular disease (Table 3). Whether better management of BP during pregnancy will lead to lower rates of morbidity related to hypertension in the immediate postpartum period is not known. Traditional CVD risk factors (e.g. obesity, hypertension, diabetes, hyperlipidemia) are associated with increased risk of HDP,[79] but the associations between HDP and future CVD, renal disease and vascular dementia, persist, even after adjustment for such factors.[34, 39 37] It is estimated that approximately two thirds of HDP-associated CVD risk is mediated via established risk factors, and the remainder likely explained by a HDP-specific etiology.[25, 33] Whether treatment of non-severe hypertension is beneficial for preventing long term morbidity beyond pregnancy and the puerperium, remains to be demonstrated. Further, evidence is needed to clarify concerns over the observed, albeit non-statistically significant, trend towards increased small for gestational age risk and decreased preterm birth in women with tight vs. less tight BP control in CHIPS.[170] Limited, though reassuring information regarding possible risk of drug associated fetal malformations, long-term neurodevelopmental effects on offspring,[171] and the suggested differential effects on these outcomes by antihypertensive class[155, 172] are all areas that require further investigation.

Given new developments in the field of hypertension outside of pregnancy that support lower BP treatment targets, together with emerging data from larger clinical trials in pregnancy, this working group supports continued investigation to determine whether BP levels similar to those recommended outside of pregnancy for initiation of therapy and as therapeutic targets are beneficial for the mother, and safe and beneficial for the fetus. While awaiting more conclusive data and trials nearing completion, we endorse informed decision making in partnership with the patient as to whether or not to treat non-severe hypertension during pregnancy to targets similar to those recommended in non-pregnant individuals. Personalization of therapy, by giving special attention to other risk factors related to hypertension-related adverse outcomes (such as pre-existing heart or kidney disease; obesity and Black race) is a rational approach.

6.3 Antihypertensive medications

Initial antihypertensive therapy is widely established to be monotherapy with an accepted first-line drug; labetalol, or methyldopa. Some,[1, 112, 144–146, 150, 152] but not all,[151] societies support the use of nifedipine as an initial therapy. For countries where labetalol is unavailable (e.g., Germany), alternative beta-blockers such as metoprolol or oxprenolol can be considered. These therapeutic options are based on small individual trials and are advocated by national and international clinical practice guidelines. There is no clear evidence that one drug is preferable to another based on systematic review of randomized trials for all types of pregnancy hypertension considered together, for all antihypertensives considered together, or for beta-blockers (including labetalol) considered separately.[155] However, in a separate network meta-analysis, specifically for treatment of chronic hypertension, atenolol was associated with fetal growth restriction,[173] especially when given for a longer duration.[174] These data conflict with some observational studies that have associated beta-blocker treatment (including labetalol) with an excess of small for

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gestational age infants, although authors did not necessarily adjust for treatment indication and severity of maternal disease.[175] These conflicting data underscore a need for more fetal and newborn data on the safety of currently used antihypertensive agents in pregnancy.

Numerous clinical trials have compared various short acting antihypertensives in the setting of acute, severe hypertension in pregnancy. The drugs most commonly examined are parenteral hydralazine, parenteral labetalol, and oral nifedipine (short, intermediate or long acting). A Cochrane review concluded that these drugs were comparable with respect to safety and efficacy, and recommended that providers choose on the basis of experience and familiarity with a particular drug.[176] Most cases of severe hypertension can be successfully controlled with these drugs using doses and protocols recommended by professional societies.[177] In resource-poor countries, a report documented successful treatment of acute severe hypertension with oral preparations of labetalol, intermediate acting nifedipine, and methyldopa.[178] Additional agents that may be considered for resistant hypertension, although not extensively studied, include nicardipine, clonidine, and furosemide.[179–181] Notably, diuretics, the mainstay of hypertension treatment in non-pregnant individuals, are not used often in pregnant women. This position is mainly informed by earlier studies suggesting that women with preeclampsia have lower plasma volume suggesting that diuretics may further aggravate volume depletion and promote reactive vasoconstriction. However, older studies demonstrated their favorable safety profile in pregnancy[182] and more recent guidelines have acknowledged that in women with salt sensitive chronic hypertension, or chronic kidney disease and reduced GFR, diuretics may be used safely although perhaps at lower doses.[2] Recent studies demonstrate that they may be particularly effective in postpartum hypertension.[134]

The limitations of existing data regarding the safety of antihypertensives in pregnancy are highlighted by a systematic review of studies addressing *in utero* exposure to antihypertensive medications and adverse fetal outcomes. Only 5 of 47 studies were considered high quality, few studies reported increased odds of adverse effects in treated compared to normotensive untreated women, including congenital malformations, and effects were not uniformly observed across different studies using the same medications.[171] Further, similar adverse events have been reported in untreated hypertensive women, leading to the conclusion that the evidence for teratogenicity of most antihypertensive agents is weak.[183, 184]

While it is first trimester exposure to medication that raises concern about structural malformations (other than those due to physical or vascular disruption), the fetal central nervous system develops throughout gestation and may be affected by exposures at any time point. However, no firm conclusions can be drawn regarding long-term child outcomes given the paucity of relevant high-quality studies.[171] No adverse neurodevelopmental effects have been observed for methyldopa,[185] nifedipine,[186] or atenolol,[187] although atenolol should be used with caution (see above). Registry data adjusted for important covariates were reassuring about the effects of preeclampsia itself; only a minimal effect was seen on standardized mathematics test scores in children from affected pregnancies at ages 9, 12, and 15 years.[188] Also, when untreated or treated hypertension controls have been used, children from labetalol and methyldopa-treated women had similar IQ scores.[2, 16, 161, 189, 190] Small

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clinical trials and observational studies suggest that amlodipine, clonidine and thiazide diuretics are probably safe in pregnancy as well.[191–193] It is also widely accepted that all renin angiotensin system blockers should be avoided during pregnancy,[194] especially during the second and third trimesters when blockade of the fetal renin angiotensin system clearly interferes with kidney development and function. Given suboptimal, and, frequently, contradicting data regarding fetal safety after exposure to antihypertensive medications *in utero*, well-designed, carefully controlled trials are needed, with attention given to short and long-term fetal as well as maternal outcomes. Finally, the providers in the field should be familiar with services offered by The Organization of Teratology Information Specialists.[195] The organization was founded in 1987 as a way of connecting experts in the field of birth defects research to the general public. It provides up-to-date information about the risks of medications during pregnancy and breastfeeding to patients, health care professionals, and researchers in the field of teratology.

7.0 Postpartum screening

International guidelines, including the ACOG, ISSHP, ESC and AHA, emphasize the need for appropriate postpartum screening and control of cardiovascular risk factors for women with a history of preeclampsia. However, the lack of studies demonstrating efficacy and effectiveness of counseling and interventions in formerly preeclamptic women impedes the development of evidence-based guidelines. The recommendations given by different guidelines are vague and imprecise (Table 6). Randomized trials are needed to evaluate potential long-term cardiovascular benefits of early initiation of statins, aspirin, or renin angiotensin system blockers in women with only a history of HDP as a risk factor. Lifestyle interventions addressing obesity, hypertension, and dyslipidemia are good clinical practices. Studies demonstrating the efficacy of these interventions in women of reproductive age are also needed.

8.0 Multidisciplinary team approach

Management of hypertension in pregnancy requires multidisciplinary collaborations among obstetricians, maternal fetal medicine specialists, neonatologists, nephrologists and hypertension specialists, cardiologists, anesthesiologists, pharmacists, nurses and midwives – all of whom contribute to providing cohesive and safe preconception, ante-, peri- and postpartum care. In particular, nurses and midwives in case management roles coordinate care and facilitate access to resources and services that improve health outcomes, such as group prenatal care,[196] economic vulnerability and chronic stress risk assessments, medication adjustments, lifestyle advice and patient education. During hospital admission, nursing recognition of maternal compromise using early warning scores,[197] hypertension bundles and toolkits ensures timely communication with a physician or advanced practice nurse and has been shown to reduce maternal mortality from hypertensive disorders.[198]

9.0 Hypertension in pregnancy and racial disparities

Maternal mortality within the U.S. is among the highest of high income countries, with a maternal mortality ratio (MMR) of 18 per 100,000 live births.[199] Within the U.S.,

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racial maternal health disparities are unacceptably large. The estimated MMR in 2016 for Caucasian women was 13 per 100,000 live births; 30 for American Indian and Alaskan Native women and 41 for Black American women, similar to that of an upper-middle income country.[200] In addition to having poorer social determinants of health, implicit racial bias is present within the U.S. health care system, and management of severe maternal morbidity is consistently worse for Black and American Indian and Alaskan Native women.[201] Hypertensive disorders of pregnancy disproportionally affect Black and American Indian and Alaskan Native women,[200, 202, 203] predominantly due to the overall higher prevalence of CVD risk factors,[204] but there is also evidence to suggest biological factors (e.g., specific genetic variants) may increase the risk of preeclampsia for Black women.[205, 206] Furthermore, preeclampsia-related severe morbidity and mortality are higher for Black women, while for Hispanic women, pregnancy outcomes tend to be better than those of Black or Caucasian women of similar risk.[207, 208]

Studies must include sufficient numbers of participants from all racial groups, especially Black women, to address maternal health disparities and inform policy and clinical practice. We endorse studies addressing prevention of shared risk factors for HDP and CVD, and those aiming to improve antenatal and postnatal outcomes.

10.0 Conclusion and future directives

Evidence suggests that antihypertensive therapy for pregnancy hypertension of any type halves the incidence of severe hypertension. To some, if not many, this is sufficiently compelling to dictate a change in practice towards more aggressive treatment. This may be of particular importance in under-resourced communities with less experience and low capacity to respond to hypertensive urgencies/emergencies. Of high income countries the USA has one of the highest hypertensive related maternal mortality,[12] and increasing maternal morbidity and mortality from cardiovascular conditions and cerebrovascular accidents.[10, 11] A lower treatment threshold than currently proposed by ACOG, has the potential to decrease serious hypertensive end-organ complications. The view that mild to moderate hypertension of short duration during pregnancy is not harmful to the mother, may be partly addressed by the Chronic Hypertension and Pregnancy study, a trial that will extend observations made in earlier trials of women with chronic hypertension which demonstrated normalization of BP with antihypertensive treatment did not adversely affect fetal growth or neurodevelopmental outcomes. Based on existing data, physicians are encouraged to individualize treatment decisions, taking other risk factors into account. Future clinical trials should address questions regarding the optimal BP treatment thresholds and should be adequately powered to assess the effects of different BP targets on maternal and fetal/neonatal outcomes. Of note, when HDP was reclassified using the lower ACC/AHA diagnostic threshold (SBP≥130 mm Hg or DBP ≥80 mm Hg), results indicated that using the lower diagnostic threshold for hypertension in pregnancy may better identify women at risk for developing preeclampsia and pregnancies at risk for adverse fetal/neonatal outcomes.[209]

Studies are also needed to determine adequate levels of BP control in the postpartum period given that first, there are no longer reservations about the impact of BP treatment on the

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fetus, second, significant maternal morbidity and mortality occurs during this time period, and third, prolonged postpartum in-hospital stay and readmissions, have a significant impact on health care resources and birth experiences.

Treatment of hypertension, prevention of seizures, and timed birth with close fetal monitoring are currently the main therapeutic options for women with preeclampsia. The superiority of any of the widely used antihypertensive(s) has not been demonstrated, and combination therapies have not been tested. While a ‘same drug for all’ approach is practical in many settings, a more personalized approach, based on patient preferences, age, race, heart rate, BP variations measured at home or in clinic, or more detailed hemodynamic assessments, may be more effective in protecting women from complications of hypertensive pregnancies and possible post-pregnancy CVD consequences. Ongoing research addressing causative pathways has the potential to identify new biomarkers and novel therapeutics that target fundamental mechanisms of preeclampsia.

Finally, on a global level, evidence-based consensus on diagnostic and treatment thresholds (such as ≥ 140/90 mm Hg), targets (keeping it below 140/90 mm Hg), long-term CVD risk assessment and HDP terminology are needed to facilitate progression in the field and importantly ensure all women worldwide receive optimal care, before, during and after pregnancy. Future guidelines should avoid integration of historical, unsubstantiated perspectives which impede improvements in women’s health during pregnancy and throughout women’s reproductive lives.

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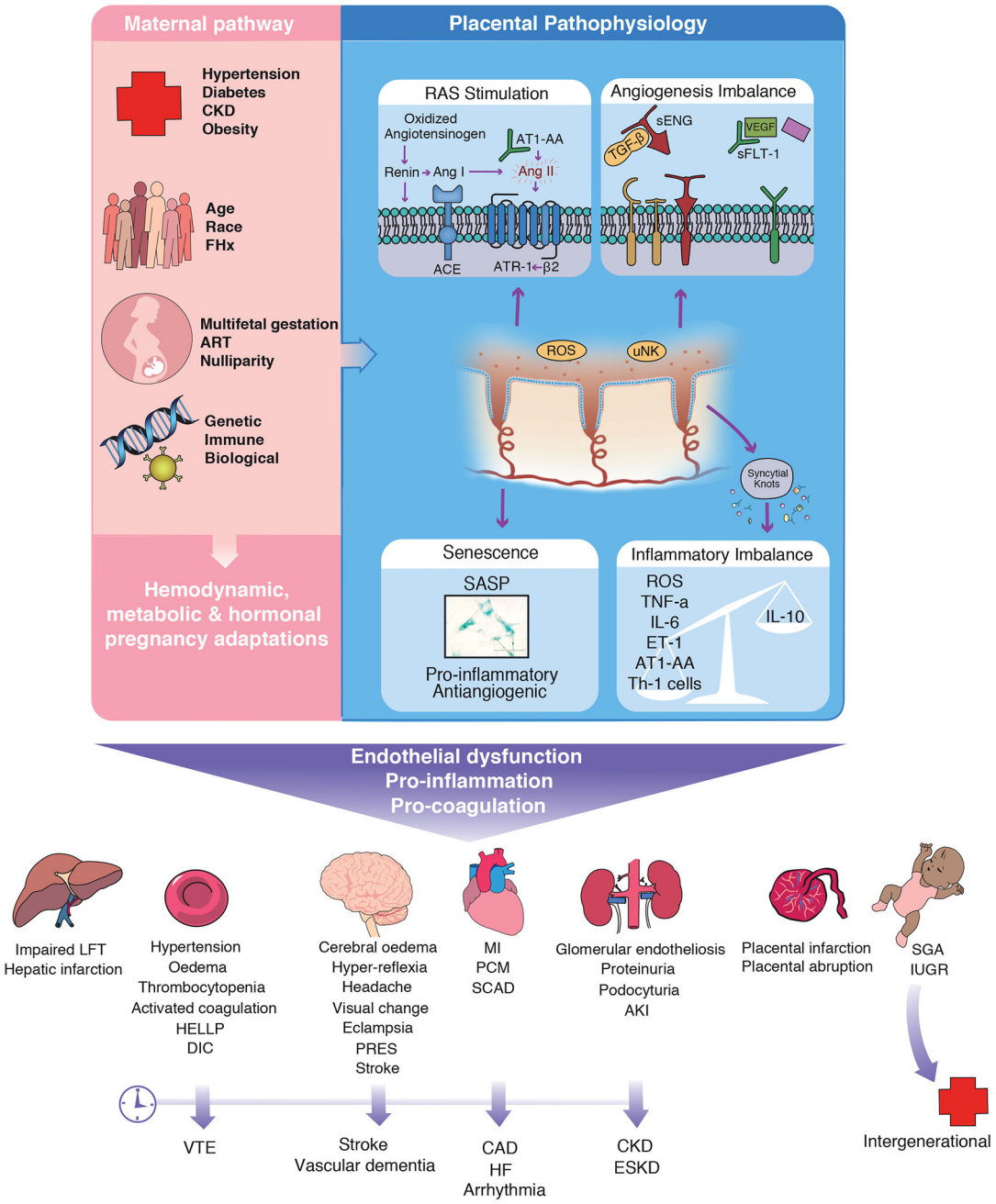

Figure 1: Pathogenesis of hypertensive disorders of pregnancy

Pre-existing maternal co-morbidities, non-modifiable patient characteristics, reproductive history, genetic and immune factors increase the risk of developing a HDP (hypertensive disorder of pregnancy). The molecular and pathophysiological mechanisms of preeclampsia are largely unknown, but the etiology is likely a combination of, and interaction between, factors from both maternal and placental pathways.[63] Variable contributions of the underlying maternal and placental pathophysiological pathways result in the heterogeneous phenotypes of HDP. The associated widespread endovascular damage and dysfunction may be long-lasting with a possible intergenerational effect.

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TPR, total peripheral resistance; CO, cardiac output; GFR, glomerular filtration rate; ROS, reactive oxygen species; uNK, uterine natural killer cell; sFlt1, soluble fms-like tyrosine kinase 1; sENG, soluble endoglin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; IL-10, Interleukin 10; Th-1, Type 1 T helper cell; AT1-AA, angiotensin II receptor 1 autoantibodies; ET-1,endothelin-1; TNF-α, tumor necrosis factor alpha; SASP, senescence-associated secretory phenotype; RAS, renin angiotensin system; Ang I, Angiotensin I; Ang II, Angiotensin II; ACE, Angiotensin converting enzyme; ATR1, Angiotensin II type 1 receptor; DIC, disseminated intravascular coagulation; VTE, venous thromboembolism; PRES, posterior reversible encephalopathy syndrome; MI, myocardial infarction; PCM, peripartum cardiomyopathy; SCAD, spontaneous coronary artery dissection; CAD, coronary artery disease; HF, heart failure; AKI, acute kidney injury; CKD, chronic kidney disease; ESKD end stage kidney disease; SGA, small for gestational age; FGR, fetal growth restriction.

Podocyturia: the urinary loss of podocytes (glomerular epithelial cells) in preeclamptic women contributes to the development of proteinuria and has been documented both before and at the time of preeclampsia diagnosis.[64]

Senescence: an irreversible cell-cycle arrest mechanism that leads to systematic metabolic and functional decline and which may play a role in impaired angiogenesis in preeclampsia.[65]

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Table 1.

American College of Obstetricians and Gynecologists definitions for Hypertensive Disorders of Pregnancy[1, 2]

Hypertensive Disorder	Definitions
Hypertension in pregnancy	Systolic BP ≥140, or diastolic BP ≥ 90 mm Hg, or both measured on 2 occasions at least 4 hours apart
Severe-range hypertension	Systolic BP ≥160, or diastolic BP ≥110 mm Hg, or both measured on 2 occasions at least 4 hours apart (unless antihypertensive therapy initiated before this time)
Chronic hypertension	Hypertension diagnosed or present before pregnancy, or before 20 weeks of gestation; or hypertension that is diagnosed for the first-time during pregnancy and that does not resolve in the postpartum period
Gestational hypertension	Hypertension diagnosed after 20 weeks of gestation and a previously normal BP
Chronic hypertension with superimposed preeclampsia	Preeclampsia in a woman with a history of hypertension before pregnancy, or before 20 weeks of gestation
Preeclampsia	Hypertension in pregnancy >20 weeks of gestation and previously normal BP or severe range hypertension, in addition to at least 1 of the following: • Proteinuria (≥300 mg/24-hour urine, or PCR ≥0.3, or dipstick 2+ only if other quantitative methods not available) • Renal insufficiency (creatinine > 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease) • Thrombocytopenia (<100× 10^9/L) • Impaired liver function (ALT/AST ≥ 2x upper limit of normal) • Pulmonary edema • New-onset headache or visual disturbances (not due to alternative diagnoses)
Preeclampsia with severe features	• Severe range hypertension (Systolic BP ≥160, or diastolic BP ≥110 mm Hg, or both) • Renal insufficiency (creatinine > 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease) • Thrombocytopenia (<100× 10^9/L) • Impaired liver function (ALT/AST ≥ 2x upper limit of normal) • Severe persistent right upper quadrant or epigastric pain unresponsive to medications • Pulmonary edema • New-onset headache or visual disturbances (not due to alternative diagnoses)

BP, blood pressure; PCR, protein creatinine ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase

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Table 2.

Immediate maternal and fetal complications of Hypertensive Disorders of Pregnancy

Maternal Outcome	**Effect estimate (95% confidence interval)**
Mortality	
Chronic hypertension	aOR 1.7 (1.2–2.4)[15]
Preeclampsia	OR 2.7 (1.0–7.1) *[16]
	aOR 2.6 (2.1–3.4)[17]
Preeclampsia superimposed on chronic hypertension	aOR 2.3 (1.5–3.6)[17]
Myocardial infarction	
Chronic hypertension	aOR 3.4 (2.2–5.1)[17]
Gestational hypertension	aOR 1.0 (0.5–2.2)[17]
Preeclampsia	aOR 3.0 (2.0–4.6)[17]
Preeclampsia superimposed on chronic hypertension	aOR 5.2 (3.1–8.7)[17]
Stroke	
Chronic hypertension	aOR 3.4 (2.8–4.1)[17]
Gestational hypertension	aOR 1.4 (1.1–1.8)[17]
	aOR 1.6 (1.1–2.3)[18]
Preeclampsia	aOR 5.7 (5.0–6.5)[17]
	aOR 7.1 (5.3–9.6)[18]
Preeclampsia superimposed on chronic hypertension	aOR 7.8 (6.3–9.8)[17]
Eclampsia	aOR 65.9 (43.6–99.6)[18]
Peripartum cardiomyopathy	
Hypertensive disorder of pregnancy	aOR 3.2 (2.1–4.9), White women[19]
	aOR 4.0 (2.3–7.1), Black women[19]
	aOR 3.0 (1.3–7.0), Hispanic women[19]
Preeclampsia superimposed on chronic hypertension	aOR 4.4 (3.6–5.3)[17]
Preeclampsia	aOR 3.3 (2.9–3.7)[17]
Gestational hypertension	aOR 1.7 (1.5–2.1)[17]
Chronic hypertension	aOR 3.8 (3.3–4.3)[17]
SCAD	7.6% higher prevalence of preeclampsia in women with SCAD vs. U.S. women of childbearing age[20]
Fetal/Neonatal outcomes	**Effect estimate (95% confidence interval)**
SGA (birth weight <10th centile)	
Hypertensive disorder of pregnancy	RR 1.6 (1.5–1.6)[21]
Severe hypertension	OR 1.8 (1.2–2.6)[22]
Preeclampsia	OR 1.5 (1.0–2.2)[22]
Still birth	
Hypertensive disorder of pregnancy	RR 1.4 (1.1–1.8)[21]
Chronic hypertension	aOR 1.7 (1.6–1.8)[17]
Preeclampsia	aOR 1.3 (1.2–1.3)[17]

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Preeclampsia superimposed on chronic hypertension	aOR 1.8 (1.7–1.9)[17]
Preterm delivery (<37 weeks)	
Chronic hypertension	aOR 1.3 (1.2–1.3)[17]
Severe hypertension	OR 2.6 (1.8–3.7)[22]
Preeclampsia	OR 3.5 (2.5–4.9)[22]
	aOR 3.1 (3.0–3.1)[17]
Preeclampsia superimposed on chronic hypertension	aOR 4.7 (4.5–4.8)[17]
Preterm delivery (<34 weeks)	
Severe hypertension	OR 3.1 (2.0–4.8)[22]
Preeclampsia	OR 2.6 (1.6–4.2)[22]
Placental abruption	
Chronic hypertension	aOR 1.4 (1.4–1.5)[17]
Gestational hypertension	aOR 1.1 (1.1–1.2)[17]
Preeclampsia	aOR 2.3 (2.2–2.3)[17]
Preeclampsia superimposed on chronic hypertension	aOR 2.2 (2.1–2.4)[17]
Postpartum hemorrhage	
Chronic hypertension	aOR 1.3 (1.2–1.3)[17]
Gestational hypertension	aOR 1.5 (1.4–1.5)[17]
Preeclampsia	aOR 2.3 (2.2–2.4)[17]
Preeclampsia superimposed on chronic hypertension	aOR 1.7 (1.6–1.7)[17]

* The study endpoint was a composite of mortality and other serious complications

Effect estimates are unadjusted unless specified as aHR/aOR. Different studies have adjusted for different variables; for specifics, please refer to the original references. Comparison groups are women who had normotensive pregnancies.

SCAD, spontaneous coronary artery dissection; SGA, small for gestational age; OR, odds ratio; RR, risk ratio; a, adjusted.

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Table 3.

Long-term maternal and off-spring complications of Hypertensive Disorders of Pregnancy

Maternal Outcome	Effect estimate (95% confidence interval)
Hypertension (≥140/90 mm Hg)	
Hypertensive pregnancy disorder	HR 2.3 (1.9–2.8)[23] OR 11.6 (10.6–12.7)[25]
Preeclampsia	aHR 4.5 (4.3–4.6)[26] aHR 2.2 (2.1–2.3)[26] RR 3.1 (2.5–3.9)[27] RR 3.7 (2.7–5.1)[28] OR 3.4 (3.1–5.0)[29]
Type 2 Diabetes	
Hypertensive pregnancy disorder	HR 1.8 (1.5–2.1)[23] HR 2.0 (1.7–2.4)[25] HR 1.4 (1.3–1.7)[30]
Preeclampsia	aHR 1.8 (1.6–1.9)[26] OR 2.14 (1.5–3.0)[29]
Hyperlipidemia	
Hypertensive pregnancy disorder	HR 1.3 (1.4–1.5)[23] HR 1.5 (1.3–1.7)[25]
Preeclampsia	aHR 1.3 (1.3 to 1.4)[26]
Sub-clinical markers of vascular damage	
Augmentation index	Weighted mean difference 5.5 % (1.6–9.4)[31]
Carotid intima-media test	Weighted mean difference 0.02 mm (0.00–0.04)[31] > 0.77 mm, aOR 3.2 (1.1–9.1)[32]
Carotid–femoral pulse wave velocity	Weighted mean difference 0.6 m/s (0.2–1.1)[31]
Arterial stiffness index	Unadjusted difference 0.32 m/s (0.13–0.51)[25]
Cardiovascular disease[†]	
Gestational hypertension	aHR 1.4 (1.1–1.9) [*][33] OR 1.7 (1.3–2.2)[24]
Preeclampsia	aHR 1.7 (1.3–2.1)[33] HR 1.7 (1.6–1.8)[34] OR 1.7 (2.5–3.0)[24]
Preeclampsia with severe features	OR 2.7 (2.5–3.0)[24]
Early onset preeclampsia (<34 weeks of gestation)	aHR 4.9 (3.0–7.8)[35] OR 5.6 (1.5-21.4)[29]
Coronary heart disease	
Hypertensive pregnancy disorder	aHR 1.9 (1.4–2.5)[33] HR 1.7 (1.3–2.3)[23] HR 1.6 (1.1–2.2)[25]
Preeclampsia	aHR 2.1 (1.5–3.0)[33] HR 1.7 (1.5–1.8)[34] RR 2.5 (1.4–4.4)[36]
Heart failure	
Hypertensive pregnancy disorder	aHR 1.5 (1.3–1.9)[34] HR 2.7 (1.6–4.6)[23] HR 2.4 (1.3–4.2)[25]

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Preeclampsia	aHR 2.1 (1.6–2.8)[34] aHR 2.0 (1.1–3.7)[33] RR 4.2 (2.1–8.4)[36]
Atrial Fibrillation	
Hypertensive pregnancy disorder	HR 1.4 (1.1–1.6)[23]
Preeclampsia	aHR 1.7 (1.4–2.2)[34]
All stroke	
Hypertensive pregnancy disorder	aHR 1.8 (1.6–2.1)[34] HR 1.9 (1.3–2.6)[23]
Preeclampsia	aHR 1.9 (1.5–2.4)[34] aHR 1.5 (1.1–2.1)[33] RR 1.8 (1.3–2.6)[36]
Ischemic hemorrhage	aHR 1.7 (1.4–2.1)[34]
Intracerebral hemorrhage	aHR 1.7 (1.2–2.4)[34]
Subarachnoid hemorrhage	aHR 2.0 (1.6–2.5)[34]
Vascular dementia	
Gestational hypertension	aHR 3.0 (2.1–4.3)[37]
Preeclampsia	aHR 2.4 (1.8–3.2)[37] HR 3.5 (2.0–6.1)[38]
Chronic kidney disease	
Gestational hypertension	RR 1.5 (1.1–2.0)[39]
Preeclampsia	RR 2.3 (1.5–3.5)[39]
End stage kidney disease	
Gestational hypertension	RR 3.6 (2.3–5.7)[39]
Preeclampsia	RR 6.6 (2.7–14.8)[39]
Venous thromboembolism	
Hypertensive pregnancy disorder	HR 1.5 (1.2–1.9)[25]
Gestational hypertension	aHR 1.4 (1.3–1.5)[40]
Preeclampsia	aHR 1.6 (1.4–2.0)[40]
Offspring Outcome	**Effect estimate (95% confidence interval)**
Cardiovascular disease[≠]	
Severe preeclampsia, term delivery	aHR 2.3 (1.1–4.7)[41]
Stroke	
Preeclampsia	HR 1.9 (1.2–3.0)[42]
Gestational hypertension	HR 1.4 (1.0–1.8)[42]
BMI	
Preeclampsia	Mean difference 0.36 kg/m^2 (0.04–0.68)[43]
Hypertension (≥140/90 mm Hg)	
Preeclampsia	SBP 5.2 mm Hg (1.6–8.7)[44] DBP 4.1 mm Hg (0.7–7.4)[44]
Gestational hypertension	SBP 2.0 mm Hg (1.4–2.7)[45] DBP 1.1 mm Hg (0.6–1.5)[45]

[*] Chronic hypertension was included as a CVD endpoint in this study.

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† Cardiovascular disease includes ischemic / hypertensive heart disease or stroke

‡ Cardiovascular disease included cardiomyopathy, hypertension, pulmonary heart disease, arrhythmia or heart failure.

All effect estimates are unadjusted unless specified as aHR. Different studies have adjusted for different variables; for specifics, please refer to the original references. Comparison groups are women who had normotensive pregnancies.

BMI; body mass index, SBP, systolic blood pressure; DBP diastolic blood pressure, HR; hazard ratio, OR; odds ratio, RR; risk ratio, a; adjusted.

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Table 4.

Risk factors for Preeclampsia

Risk Factors	Effect estimate (95% confidence interval)
High *	
Prior preeclampsia	RR 8.4 (7.1–9.9)[79]
Chronic stage 2 hypertension † (≥140/90 mm Hg)	RR 5.1 (4.0–6.5)[79]
Pre-gestational diabetes	RR 3.7 (3.1–4.3)[79]
Multi-fetal pregnancy	RR 2.9 (2.6–3.1)[79]
Antiphospholipid syndrome	RR 2.8 (1.8–4.3)[79]
Systemic lupus erythematosus	RR 2.5 (1.0–6.3)[79]
Chronic kidney disease	OR 10.4 (6.3–17.1)[80]
Moderate *	
Maternal age >35 years	RR 1.2 (1.1–1.3)[79]
Pre-pregnancy BMI >30	aOR 3.7 (3.5–3.9)[81] RR 2.8 (2.6–3.1)[79]
Family history (1st degree relative)	RR 2.9 (1.7–4.9)[82]
Race (Black)	aHR 1.6 (1.5–1.6)[83] HR 2.2 (1.9–2.6), early onset[84] HR 1.3 (1.2–1.4), late onset[84]
Low socioeconomic status	aOR 4.91 (1.9–12.5)[85]
Nulliparity	RR 2.1 (1.9–2.4)[79]
History of adverse pregnancy outcome:	
Stillbirth	RR 2.4 (1.7–3.4)[79]
Placental abruption	RR 2.0 (1.4–2.7)[79]
Other	
Chronic hypertension (130–134/80–84 mm Hg)	aOR 2.2 (1.9–2.5), mild[86]
	aOR 2.7 (2.0–3.5), severe[86]
Chronic hypertension (135–139/85–90 mm Hg)	aOR 2.7 (2.3–3.2), mild[86]
	aOR 3.8 (2.8–5.1), severe[86]
White coat hypertension	RR 2.4 (1.2–4.8)[87]
Severe hypertension	OR 6.1 (4.4–8.5)[22]
Pre-pregnancy BMI >25	RR 2.1 (2.0–2.2)[79]
Insulin resistance >75th centile, Gestational diabetes	aOR 1.9 (1.1–3.2)[88]
	aOR 1.6 (1.4–1.9)[89]
Recovered acute kidney injury	aOR 2.9 (1.9–4.4)[90]
Hyperthyroidism	aOR 1.8 (1.1–2.9)[91]
Hydatidiform mole	OR 10.1 (3.4–30.0)[92]
Trisomy 13 fetus	Incidence, Trisomy 13 24–44% vs. without 2–8%[93]
Genetic susceptibility[94, 95]	
Assisted reproductive technology	RR 1.8 (1.6–2.1)[79]

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Risk Factors	Effect estimate (95% confidence interval)
Oocyte donation	OR 4.3 (3.1–6.1)[96]
New paternity	OR 2.3 (1.2–4.4)[97]
Pregnancy interval >4 years	OR 1.1 (1.0–1.2), recurrent preeclampsia[98]
	OR 2.1 (1.3–3.3)[97]
Migraine	OR 2.1 (1.5–2.9)[99]

*Classification of risk factors as high or moderate is based on the ACOG recommendations for aspirin therapy to prevent preeclampsia. Therapy is indicated when ≥ 1 high or ≥ 2 moderate risk factors are present.[77, 100]

Others are based on an emerging number of factors that may increase risk of preeclampsia.

†Based on the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults[6]

Cohabitation of >12 months[101] and smoking[102, 103] have an inverse association with preeclampsia risk.

All estimates are unadjusted unless specified as aHR/aOR. Different studies have adjusted for different variables; for specifics, please refer to the original references. Comparison groups are women without the risk factor of interest.

BMI, body mass index; HR; hazard ratio, OR; odds ratio, RR; relative risk.

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Table 5.

Secondary causes of hypertension in pregnancy among young women

Diagnosis	Clinical Features	Laboratory Features	Pregnancy Outcomes	Treatment/ Management
Chronic Kidney Disease	Edema Hypertension	Proteinuria Hematuria Decreased eGFR	Preeclampsia Pre-term birth IUGR	Antihypertensives Low dose aspirin
Primary Hyperaldosteronism	Postpartum HTN exacerbation	Hypokalemia Suppressed PRA	Preeclampsia risk increased	Calcium channel blockers Labetalol Thiazide diuretics Potassium supplementation
Renovascular Hypertension	Resistant HTN Abdominal bruit	Elevated PRA	Preeclampsia Pre-term birth	Antihypertensives Angioplasty in second trimester
Pheochromocytoma	Hypertension Tachycardia	Elevated plasma + urine metanephrines or catecholamines	Severe hypertension Fetal + maternal mortality	MRI without gadolinium Alpha blockade Calcium channel blockers Surgery in second trimester
Cushing's Disease	Gestational diabetes Abdominal striae Hypertension	Urinary free cortisol Late night salivary cortisol High dose dexamethasone suppression test	Preeclampsia Pre-term birth IUGR Fetal mortality	Metyrapone Surgery
Obstructive Sleep Apnea	Hypertension Apnea Fatigue Headaches Depression	Deranged polysomnography Desaturation Elevated HbA1c Elevated EPO	Preeclampsia Pre-term birth	CPAP Oral mandibular repositioning devices

eGFR, estimated glomerular filtration rate; IUGR, intrauterine growth restriction; HTN, hypertension; PRA, plasma renin activity; MRI, magnetic resonance imaging; HbA1c, glycated hemoglobin; EPO, erythropoietin; CPAP, continuous positive airway pressure.

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Table 6.

Summary of and key discrepancies between published guidelines for the diagnosis and treatment of hypertensive disorders of pregnancy

Guideline		HYPERTENSION IN PREGNANCY Diagnosis*	Treatment threshold (mm Hg)	Treatment target (mm Hg)	Continuation of anti-hypertensive therapy
American College of Obstetricians and Gynecologists	2013[1] 2019[2] 2020[3]		≥ 160/105 with diagnosis of chronic hypertension[1] ≥ 160/110 if acute[3]/chronic hypertension[2] †	120–159/80–105[1] 120–159/80–109 if chronic[2] †	Guided by informed discussion with women
World Health Organisation	2018[144] 2020[145]	Not defined	Not specified ‡	Above lower limits of normal[145]	Not specified
National Institute for Health and Clinical Excellence	2019[146]		≥ 140/90	≤135/85	Continue treatment unless <110/70 mm Hg or symptomatic hypotension
Society of Obstetricians and Gynaecologists, Canada	2018[147] 2020[148]		≥ 140/90[148, 149]	DBP 85[148, 149] <140/90 + comorbidities[149]	Not specified
International Society for the Study of Hypertension in Pregnancy	2018[112]	+ the absence of preeclampsia features	≥ 140/90 in office ≥ 135/85 at home	110–140/85	Not specified
European Society of Cardiology	2018[150]	"Antenatally unclassified" if first BP measure > 20 weeks of gestation	≥ 150/95 ≥ 140/90 + end-organ damage / gestational hypertension	Not specified	Consider discontinuation if BP 140–159/90–109 mm Hg + normal renal function
Society of Obstetric Medicine of Australia and New Zealand	2014[151]		≥ 160/100 ≥ 140/90, optional	Based on clinician assessment	Consider discontinuation if BP fall <20 weeks of gestation

Guideline		PREECLAMPSIA Diagnosis §	SUPERIMPOSED PREECLAMPSIA ON CHRONIC HYPERTENSION Diagnosis §	Treatment threshold (mm Hg)	Treatment target (mm Hg)
American College of Obstetricians and Gynecologists	2019[1]		Chronic hypertension + a sudden change in preeclampsia diagnostic parameters	≥ 160/110[1]	Not specified
National Institute for Health and Clinical Excellence	2019[146]	Symptoms include utero-placental dysfunction //	Not specified	≥ 140/90	≤ 135/85
Society of Obstetricians and Gynaecologists, Canada	2014[149] 2018[152]	Symptoms include ≥1 severe complication	≥ 20 weeks of gestation + resistant hypertension + new or worsening proteinuria or ≥1 adverse conditions or severe complications of preeclampsia	≥ 140/90[152]	DBP 85[152]
International Society for the Study of Hypertension in Pregnancy	2018[112]	Symptoms include utero-placental dysfunction‡	Chronic essential hypertension + ≥ 1 sign of maternal organ dysfunction consistent with preeclampsia, or new-onset proteinuria in the setting of a rise in BP	≥ 140/90	110–140/85
European Society of Cardiology	2018[150]	Proteinuria necessary, only high suspicion if hypertension + abnormal biochemistry / symptomatic	Hypertension <20 weeks of gestation + superimposed gestational hypertension + proteinuria	≥ 140/90	Not specified

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Society of Obstetric Medicine of Australia and New Zealand	2014[151]	Symptoms include fetal growth restriction	Pre-existing hypertension with proteinuria or ≥1 systemic feature of preeclampsia	160/100 140–160 / 90–100, optional	Individual assessment

Guideline		Future cardiovascular disease risk management
American College of Obstetricians and Gynecologists	2019[153]	Postpartum follow-up visit (early postpartum visit) with either the primary care provider or cardiologist is recommended within 7–10 days of delivery for women with hypertensive disorders
National Institute for Health and Clinical Excellence	2019[146]	Referral to family care doctor for CVD risk prevention
Society of Obstetricians and Gynaecologists, Canada	2014[149]	All women who have had a hypertensive disorder of pregnancy should pursue a healthy diet and lifestyle
International Society for the Study of Hypertension in Pregnancy	2018[112]	Regular general practitioner follow-up to monitor BP + periodic measurement of fasting lipids and blood sugar. Adopt healthy lifestyle with maintenance of ideal weight and regular aerobic exercise
European Society of Cardiology	2018[150]	Annual primary care physician CVD risk screen
Society of Obstetric Medicine of Australia and New Zealand	2014[151]	Advise optimization of CVD risk factors

*SBP ≥140 mm Hg +/ DBP ≥90 mm Hg; Gestational Hypertension, > 20 weeks of gestation + previously normal BP; Chronic/pre-existing Hypertension, < 20 weeks of gestation

†American College of Obstetricians and Gynecologists guidelines state to consider a lower treatment threshold for chronic hypertension if comorbidities/renal failure are present and to consult with other subspecialties regarding antihypertensive treatment BP targets, although this is not specified in the recommendations.[2]

‡World Health Organisation recommendations state that “women with non-severe hypertension during pregnancy should be offered antihypertensive drug treatment in the context of good quality antenatal care follow-up,”[145] and “women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.”[144]

//Utero placental dysfunction: fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, stillbirth

§All guidelines require SBP ≥140 mm Hg +/ DBP ≥90 mm Hg >20 weeks of gestation + previously normal BP + ≥1 proteinuria / abnormal renal or liver function tests or platelet count / symptoms and signs consistent with end-organ damage of PE

BP, blood pressure; PE, preeclampsia; SBP, systolic blood pressure; DBP diastolic blood pressure

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